

REMARKS

Claims 32-40 and 42-44 are under consideration. Applicants amended the specification to further describe the subparts of Figures 6, 7, 11, and 12 and to identify the sequences set forth in Figures 5 and 7. These amendments do not introduce new matter, as they make express what was implicit in these figures. Applicants also submit a new Figure 5, which corrects the first amino acid in SEQ ID NO 5 from "C" to "G." As it is well known that the codon "GGG" encodes the amino acid glycine, this amendment does not add new matter. In addition, Applicants submit new Figures 7A and 7B, which corrects the third amino acid in SEQ ID NOS 47 and 49 from "D" to "G." As it is well known that the codon "GGT" encodes the amino acid glycine, this amendment does not add new matter. Applicants note that the current Sequence Listing and the Sequence Listing as originally filed contain the correct amino acid sequence. Finally, Applicants have amended claims 32 and 37 to clarify to what element the terms "fragment, region, or derivative" refer.

The Office made final the Restriction Requirement between Group I (claims 32-40 and 42-44) and Group II (claim 41). In this response, claim 41 has been withdrawn. The Office has also acknowledged Applicants' claim to priority and the consideration of the Information Disclosure Statements filed June 29, 2001, and October 7, 2002.

The Office has rejected claims 32-40 and 42-44 under the doctrine of obvious-type double patenting and under 35 U.S.C. §§ 112 and 102. Applicants note that the Office has implicitly declared independent claims 37, 42, and 43 and their dependent claims free of the prior art, as there are no outstanding rejections against these claims

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based on anticipation or obviousness. Applicants address each of the pending rejections below according to their judicial and statutory origins.

Sequence Listing and Brief Description of the Drawings

The Office alleges that the current Sequence Listing does not comply with 37 C.F.R. §§ 1.821-1.825 because Figures 5, 7A, and 7B show a plurality of sequences, only some of which are identified with a sequence identification number (SEQ ID NO). Applicants contend that the current Sequence Listing does comply with the requirements of the Federal Rules. Regarding these figures, the sequences not assigned a SEQ ID NO are identical to prior sequences in the figure that were assigned a number. Applicants have amended the description of these figures accordingly. Thus, Applicants have assigned every unique sequence in the instant application a SEQ ID NO. As the Office's objection to the current Sequence Listing has been obviated, Applicants respectfully request its withdrawal.

The Office also objects to the Brief Description of the Drawings because they do not describe the subparts of Figures 6, 7, 11, and 12. Applicants have amended the description of these figures in the specification to clarify the identity of each figure's subparts. Applicants therefore request that the Office withdraw its objection.

Rejection Under Obvious-Type Double Patenting

The Office rejects claim 32 for alleged obvious-type double patenting in light of claims 1-6 of U.S. Patent No. 5,955,074 ('074 patent). According to the Office, allowed claims 1-6 are directed to a method of treating *Staphylococcus epidermidis* infection in which the immunoglobulin used is selected against a teichoic acid antigen. Claim 32, the Office believes, is directed to a method of treating any Gram positive infection.

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Because *S. epidermidis* is a species of Gram positive bacteria, the Office concludes that claim 32 is obvious because a species anticipates a genus. Applicants respectfully traverse.

The immunoglobulin (Ig) used in independent claim 1 of the '074 patent is obtained from one of serum, plasma, and an immunoglobulin pool. These sources of Ig represent preparations that will have a wide variety of antibodies. Likewise, these Ig preparations also have a wide variety of reactivity and opsonic activity towards *S. epidermidis*. The method of claim 1 uses Ig sources that have been screened for binding to *S. epidermidis*. The Office asserts that the Ig was selected against *S. epidermidis* teichoic acid antigen, referring to the TCA antigen extraction protocol described in the '074 patent. Applicants respectfully disagree. The "TCA antigen extract" involves the extraction of bacterial antigens by trichloroacetic acid (TCA). This extract contains several hundred antigens, among them teichoic acid and lipoteichoic acid (LTA). See WO 96/09321, page 45 last full paragraph submitted herewith. Thus, though the Ig used in the method of issued claim 1 of the '074 patent is selected for specific binding to *S. epidermidis*, the Ig targets a broad spectrum of *S. epidermidis* antigens, whether in a whole cell or a TCA extract. Rather than a species, this claim can be more accurately viewed as a genus.

In contrast, pending claim 32 requires an antibody that binds to lipoteichoic acid (LTA), which is one of the many antigens on the bacteria. Accordingly, pending claim 32 is more akin to a species claim. Given the many antigens in the genus, see WO 96/09321, page 45, the genus cannot render the species obvious. Moreover, for a single antigen to give rise to antibodies that react not only with the *S. epidermidis* used

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to generate the antibody, but also with other species of Gram positive bacteria is even less obvious. For these reasons, claim 32 is not rendered obvious in light of claims 1-6 of the '074 patent and request that the Office withdraw this double patenting rejection of claim 32.

Rejections Under 35 U.S.C. §112

The Office rejects claims 32-40 and 42-44 as allegedly not enabled for the use of any monoclonal antibody (MAb), fragment, region, or derivative that binds SEQ ID NO 1 or 2 or is a derivative of SEQ ID NO 88 or 89 for treating or preventing a Gram positive bacterial infection. Applicants note with appreciation that the Office concedes that the specification is enabling for using a polyclonal antibody preparation or the specific MAb 96-110. Because claims 34, 35, 39, 40, and 44 recite MAb 96-110 specifically and the Office has indicated that the specification is enabling for the use of this MAb, this rejection should not apply to these claims. Thus, Applicants will address each of the Office's specific arguments as they relate to claims 32, 33, 36-38, 42, and 43.

First, the Office argues that the effect antibodies have on treating infections can be unpredictable, citing 5 references that allegedly demonstrate this unpredictability. Fiedel and Jackson (*Abstracts of the Ann. Mtg. of the Amer. Soc. for Microbiol.*, p. 104, abstract M146 (1972); "Fiedel") allegedly show that anti-teichoic acid antibodies induced kidney disease in rabbits. Aasjord et al. (*Acta Path. Microbiol. Immunol. Scand.*, 93:245-50 (1985); "Aasjord") allegedly discloses two anti-LTA antibodies that demonstrated equivalent binding specificities as antibodies associated with multiple sclerosis (MS). Stashenko et al. (*Archs. Oral Biol.*, 31:455-61 (1986); "Stashenko") allegedly discloses 5 MAbs against *S. mutans* LTA that enhanced adherence of that

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bacterium along with *S. salivarius*, *S. sanguis*, and *L. casei*. Wergeland et al. (*J. Clin. Microbiol.*, 27:1286-91 (1989); "Wergeland") allegedly discuss patients with staphylococcal infections that have antibodies to LTA, teichoic acid, and peptidoglycan and still have disease. Yuji et al. (*Men'eki Arerugi*, 13:50-51 (1994); "Yuji") allegedly reports that children with anti-LTA antibodies still have recurrent tonsillitis. Applicants will address each reference below.

Regarding Fiedel, Applicants suggest that the Office has misconstrued the teaching of this abstract. Fiedel used two different mBSA-teichoic acid inoculums, one with a protein:phosphate ratio of 19:1 and the other 30:1. Rabbits that received the 19:1 inoculum demonstrated kidney abnormalities. In contrast, animals that received the 30:1 inoculum had normal kidneys. Moreover, the authors report that "[a]ntibody production appeared to follow a similar course with both types of complexes." See last three lines of the abstract. Thus, because the antibody production was nearly the same with both inoculums, it was the inoculum itself and not the antibodies that were likely causing the kidney dysfunction in these rabbits. Thus, Fiedel does not stand for the proposition that antibodies to teichoic acid, a different antigen from LTA, cause kidney disease.

Regarding Aasjord, anti-LTA antibodies were found in both MS and normal patients, indicating that antibodies to this antigen are not the cause of MS pathogenesis. See Table 1. Applicants note that the authors themselves acknowledged this by noting that "[i]t is not possible to see any clear differences between the two patient groups. . . ." See left column, lines 11-13, p. 250. In the end, Aasjord speculated that antibodies from the CSF of MS patients may show a "slightly different" specificity than those from

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the normal group. Thus, Aasjord's own data and statements are at odds with the Office's conclusion that this reference links anti-LTA antibodies with the disease state of MS.

Stashenko did report an enhancement in bacterial adhesion, but the Office did not appreciate that this effect was dose-dependent. The authors tested their antibodies at three concentrations and only the highest concentration lead to an enhancement of adhesion to artificial salivary pellicles. See Abstract and Table 5. As the assay they used to test adherence was totally artificial, the authors considered what might be responsible for the dose-dependent response. They noted that bacteria secrete LTA into their environment and that LTA could coat the pellicles. Given that the authors did not wash the *S. mutans* culture that was pre-incubated with anti-LTA antibodies before adding the pellicles, free, unbound anti-LTA antibodies would be available to provide a bridge between the LTA on the pellicles and LTA on the bacterial wall. This would explain the dose-dependent effect, as lower doses would have fewer unbound anti-LTA antibodies in the pre-incubation mixture of bacteria with antibodies. See paragraph spanning pp. 459 and 460. See paragraph spanning pp. 456 and 457 for adhesion assay. Thus, by the authors' own express statements, this enhancement of bacterial adhesion may well have been an artifact of the way they performed their adhesion assay.

Regarding Wergeland, serum samples were taken from patients with verified or suspected staphylococcal infections as a snap shot of the immune response to infection at the time the serum samples were taken. Thus, these samples represent the immune response at a particular stage of that response, when the antibodies are being prepared

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and the bacteria still subsist in the host. Wergeland noted that antibodies to LTA were significantly positively correlated with total IgG in the patient sera, which is consistent with this antigen as being important to an anti-bacterial response. See p. 1288, first two paragraphs under "Correlation Coefficients" section. There is, however, no indication in the paper that the patients studied failed to resolve their infections over time and thus no teaching that anti-LTA antibodies are not important to treating or preventing Gram positive bacterial infections.

Yuji's alleged observation that children with anti-LTA antibodies are still subject to recurrent tonsillitis does not demonstrate that anti-LTA antibodies are ineffective against tonsillitis. Tonsillitis is not always caused by Gram positive bacteria in which case an anti-LTA antibody would not be expected to be useful. In addition, it is possible that these children have deficiencies in one or more of the other components of the immune system that are needed for effective antibody-mediated control of an infection, i.e., phagocytes and the complement factors. Thus, there are alternate explanations for why Yuji's observation was made.

Thus, none of these references support the Office's lack of enabling disclosure.

Second, the Office notes that SEQ ID NOS 1 and 2 share some sequence identity with other antigens in other organisms and attempts to call into question whether the antibody used in the method of the invention would be specific for LTA. Applicants note that independent claims 32, 37, 42, and 43 do not call for exclusive reactivity to LTA. The Office is reading into the claims an element which is not there. Rather, claims 32 and 37 merely require that the antibody used bind to LTA, but this does not mean that the antibodies cannot bind other antigens. Thus the Office's point

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here is irrelevant. Moreover, *arguendo*, even if the antibody used in the invention did recognize these other antigens, the potential recognition of other antigens on other potential pathogens argues for an increased benefit from the method of the invention as it could target multiple infections simultaneously.

Third, regarding claims 42 and 43, the Office believes that several Ig light chains exist that share at least 70% homology with the sequences of SEQ ID NOS 88 or 89 and provides a specific alleged example of one that satisfies the 70% homology requirement but is specific for blood factor IX. Again, as discussed above, the antibody used in the invention does not need to bind LTA exclusively; it can also bind other antigens. Furthermore, if this antibody only bound blood factor IX and did not bind LTA, then it would not fall under the scope of the invention.

Finally, the Office claims that no specific guidance has been given as to how to modify an antibody derivative or how to use an antibody fragment as a pharmaceutical composition to treat or prevent a Gram positive bacterial infection. Again the Office invokes its argument that the use of antibodies to treat infections can be unpredictable. Applicants contend that the specification gives ample guidance.

At page 19, the specification provides a description of examples of antibody fragments and correctly indicates that the methods of making such fragments are well known in the art. The skilled artisan would not have to use undue experimentation to produce such fragments based on the numerous teachings available. The antibody regions are also discussed at page 19 of the specification and include the heavy chain constant region (H_c or C_H), a heavy chain variable region (H_v or V_H), a light chain constant region (L_c or C_L), and a light chain variable region (L_v or V_L). The specification

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teaches how to chimerize a murine antibody and doing so, provides ample teaching as to how to isolate these regions. See Example 8 of the specification.

Antibody derivatives are discussed at page 21 of the specification and include proteins or peptides encoded by truncated or modified antibody genes. Given the production of a chimerized murine antibody as described in detail in the specification, it is clear that the techniques required to isolate an antibody gene and to modify it via recombinant DNA cloning techniques were well known. The skilled artisan would not have to exercise undue experimentation to generate such derivatives and to express them *in vivo* via methods akin to those in Example 9.

In sum, the specification is fully enabling for claims 32-40 and 42-44. The Office has not provided any evidence that the use of antibodies to treat Gram positive infections is unpredictable vis à vis any potential damaging effects the antibodies may have on the host. Moreover, even if the Office's analysis of whether anti-LTA antibodies were useful in preventing or treating Gram negative bacterial infections were correct, this uncertainty would only highlight the need for the instant invention further. But as discussed above, the Office failed to make even this case. Finally, the specification in combination with the very standard techniques known in the art for generating fragments, regions, and derivatives is fully enabling for claims 32-40 and 42-44. Applicants respectfully request that the Office withdraw its rejection accordingly.

Claims 32 and 37 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Specifically, the Office believes that the terms "fragment, region, or derivative" could refer to the antibody, the bacteria, or the LTA. Solely to facilitate prosecution and to clarify the claimed invention, Applicants have amended these claims

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to indicate that these terms apply to the anti-LTA antibody. As this rejection is now rendered moot, Applicants request that the Office withdraw it.

Rejections Under 35 U.S.C. §102

The Office rejects claim 32 as allegedly anticipated by Dale et al. (*J. Infect. Dis.*, 169:319-23 (1994); "Dale") under 35 U.S.C. § 102(b). The Office believes that 1. Dale discloses a method of preventing infection comprising administering a pharmaceutical composition that comprises an antibody to LTA of Gram positive bacteria; 2. that the antibodies had a binding activity twice background; and 3. that opsonization of bacteria resulted in no colonization defining evidence of opsonic activity of 75% or more. Applicants respectfully traverse.

Dale describes only one experiment addressing the ability of anti-LTA antibodies to prevent streptococcal infection. This experiment was a mortality experiment in which the authors pre-mixed streptococci bacteria with the antibodies before intranasal delivery to animals. Figure 1 showed that the treatment was able to prevent almost all mortality. When discussing these results, the authors concluded that these antibodies blocked the adherence of the bacterial to epithelial cells, an observation consistent with what prior studies had indicated. The Office has somehow read into this data that the binding of these antibodies to LTA is twice the level of background and that these antibodies have opsonic activity of 75% or greater. Applicants respectfully contend that Dale does not provide any evidence showing that their antibodies possess these traits. The Office merely assumes that a blocking antibody has the requisite binding. Further, an antibody's ability to block adherence to host cells has no bearing on its opsonic

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activity, which is controlled by a different portion of the antibody. As discussed in a common Immunology text:

The antibody molecule itself has two separable functions. One is to bind specifically to molecules from the pathogen that elicited the immune response; the other is to recruit other cells and molecules to destroy the pathogen once the antibody is bound to it. These functions are structurally separated in the antibody molecule, one part of which specifically recognizes antigen, while the other engages the effector mechanisms that will dispose of it.

Charles A. Janeway, Jr. & Paul Travers, *Immunobiology: The Immune System in Health and Disease* 3:1 (Miranda Robertson ed., Garland Publishing 1994). See generally, *id.* at 3:1-3:3 and 3:28-3:29. Thus, Dale cannot anticipate the invention of claim 32.

Applicants request that this rejection be withdrawn.

Claim 32 stands rejected as allegedly anticipated by Fischer (WO 93/19373) under 35 U.S.C. § 102(b) because the Office believes that this reference discloses the claimed method and uses a composition comprising antibodies to Gram positive bacteria. This reference does not provide any data indicating that the antibody preparations used contain an antibody that binds to LTA and that has the required binding and opsonic activities. As provided in EP 783,520 B1, this sera reacted most strongly to a protein antigen. Applicants request that this rejection be withdrawn, as this reference does not provide all the elements of claim 32.

The Office rejects claims 32 and 33 as allegedly anticipated by Fattom et al. (U.S. Patent 5,770,208; "Fattom 1") under 35 U.S.C. § 102(e). According to the Office, this reference teaches the claimed method and uses antibodies that react with a conserved sugar and two other polysaccharide antigens. Applicants note that Fattom 1

discloses one antigen, the "336 antigen," which is not identified as LTA. Given that these authors did an analysis of the antigen by gas liquid chromatography, it is likely that it would have identified the antigen as LTA if this were the case. Instead, Fattom 1 describes the antigen in general terms. See Example 4. Further, the opsonic activity displayed in Figure 2 was a measurement of antibodies developed to a conjugate vaccine of the 336 antigen and exotoxin A. See brief description of Figure 2 and Example 5. This experiment does not control for the possibility that anti-exotoxin A antibodies may give rise to the activity seen, as no *S. aureus* that does not carry the 336 antigen was used as a control. Thus, Fattom 1 does not teach a method in which a pharmaceutical composition comprising an antibody that binds to LTA and that has the requisite binding and opsonic activities.

According to the Office, claims 32 and 33 are anticipated by Gristina et al. (U.S. Patent 5,505,945; "Gristina") under 35 U.S.C. § 102(e) because this reference allegedly discloses the claimed method and uses a composition comprising antibodies to Gram positive bacteria, which antibodies allegedly prevented adhesion to a surface associated with disease. As with Dale above, Gristina measures only the ability of their antibody to block an interaction. Unlike Dale, who at least measured this on living cells, Gristina measured binding to polymethylmethacrylate (PMMA). See col. 6, lines 18-23. Thus, Gristina's results are even further removed from the instant invention which pertains to treating and preventing infections *in vivo*. As discussed above with Dale, an antibody's ability to block adherence cannot be extrapolated to mean that its binding activity is twice above background or that it will have opsonic activity. Applicants note that Gristina discusses the benefit of opsonic activity generally (see Abstract and Table

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1), but provides absolutely no data showing that their anti-RP12 sera is opsonic. Finally, Gristina does not show binding to LTA. For these reasons, Applicants request that the Office withdraw this rejection of claims 32 and 33.

Claims 32 and 33 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Fattom et al. (WO 93/09811; "Fattom 2"). According to the Office, Fattom 2 discloses the claimed method and used a composition comprising polyclonal antibodies, monoclonal antibodies, or antibody fragments that "would" react with LTA. The Office's improper assumption that the antibodies disclosed "would" react with LTA is not founded on fact, but on opinion. Applicants note that the polysaccharide antigen discussed in Fattom 2 is type-specific, meaning that the antisera generated to this antigen only recognizes antigen from the same serotype of *S. epidermidis* used to create it. See p. 4, lines 24-26. Given that this antigen makes serotype-specific antisera and will not recognize all *S. epidermidis*, it is difficult to imagine how this antigen would lead to sera that would be useful in treating or preventing a broad spectrum of Gram positive bacterial infections, even if these serotype-specific antigens were mixed into one inoculum. Moreover, Fattom 2 provides no evidence on the extent of opsonic activity, let alone the specific opsonic activity of an antibody that binds LTA. Thus, Fattom 2 does not teach all the elements of the claims 32 and 33 and cannot anticipate these claims.

The Office rejects claim 32 as allegedly anticipated by Ichiman et al. (*Microbiol. Immunol.* 33:277-86 (1989); "Ichiman") under 35 U.S.C. § 102(b). Specifically, the Office believes that Ichiman discloses the claimed method and uses antibodies to unencapsulated Gram positive bacteria. The Office concludes that because the

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bacteria are unencapsulated, they would generate antibodies to cell surface teichoic acid antigens. Applicants respectfully traverse.

First, the Office again speculates that Ichiman generated anti-LTA antibodies. The authors themselves concluded from their study that unencapsulated strains of *S. epidermidis* are capable of producing protective antigens as are encapsulated strains. See p. 285. They then acknowledge that "the biochemical properties of protective antigens of unencapsulated strains have not been elucidated . . . and these aspects remain to be clarified." *Id.* Thus, Ichiman does not make the assumption the Office is willing to make. Second, Ichiman provides no opsonic activity data for their prepared sera nor any evidence that their composition contains an antibody that recognizes LTA and has the requisite binding and opsonic activities. In sum, Ichiman does not provide all the elements of the claimed invention. Applicants request that these rejections under 35 U.S.C § 102 be withdrawn as none of the references cited by the Office anticipate claim 32 or claim 33.

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Conclusion

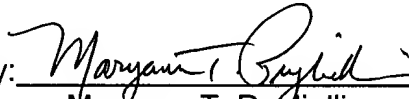
In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the claims under consideration.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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6MER.SEQ

	10	20	30	
41:13.6mer2-1	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	SEQ ID NO.4
61	G A H	A D R V	Y G A	SEQ ID NO.5
42:14.6mer2-2	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
65	G A H	A D R V	Y G A	
43:15.6mer2-3	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
66	G A H	A D R V	Y G A	
44:16.6mer2-4	GGGA-TCATG	CGGATAGGGT	TTATGGGGCC	SEQ ID NO.6
62	G ? H	A D R V	Y G A	SEQ ID NO.7
45:17.6mer2-5	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
67	G A H	A D R V	Y G A	
46:18.6mer2-6	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
68	G A H	A D R V	Y G A	
47:19.6mer2-7	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
69	G A H	A D R V	Y G A	
48:20.6mer2-8	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
70	G A H	A D R V	Y G A	
49:21.6mer2-9	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
71	G A H	A D R V	Y G A	
51:23.6mer2-11	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
72	G A H	A D R V	Y G A	
52:24.6mer2-12	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
73	G A H	A D R V	Y G A	
53:25.6mer2-13	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
74	G A H	A D R V	Y G A	
54:26.6mer2-14	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
75	G A H	A D R V	Y G A	
55:27.6mer2-15	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
76	G A H	A D R V	Y G A	
56:28.6mer2-16	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
77	G A H	A D R V	Y G A	
58:30.6mer2-18	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
78	G A H	A D R V	Y G A	
59:31.6mer2-19	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
79	G A H	A D R V	Y G A	
60:32.6mer2-20	GGGGCTCATG	CGGATAGGGT	TTATGGGGCC	
80	G A H	A D R V	Y G A	

FIG. 5

15MER1.SEQ

	10	20	30	40	50	60	
51:28.15mer1-2/0	GGGGCTGATT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	SEQ ID NO.44
67	G A D	(W) I T (F)	(H) R R	H (H) D	(R) V L S	G A	SEQ ID NO.45
52:29.15mer1-3/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	SEQ ID NO.46
68	G A G	W I T F	H R R	H H D	R V L S	G A	SEQ ID NO.47
53:32.15mer1-6/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	
65	G A G	W I T F	H R R	H H D	R V L S	G A	
62:13.15mer1-7/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	
66	G A G	W I T F	H R R	H H D	R V L S	G A	
63:14.14mer1-8/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	
67	G A G	W I T F	H R R	H H D	R V L S	G A	
64:15.15mer1-9/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	
68	G A G	W I T F	H R R	H H D	R V L S	G A	
65:16.15mer1-10/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	
69	G A G	W I T F	H R R	H H D	R V L S	G A	
56:17.15mer1-11/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	
70	G A G	W I T F	H R R	H H D	R V L S	G A	
57:20.15mer1-12/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	
71	G A G	W I T F	H R R	H H D	R V L S	G A	
58:29.15mer1-13/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	
72	G A G	W I T F	H R R	H H D	R V L S	G A	
59:20.15mer1-14/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	
73	G A G	W I T F	H R R	H H D	R V L S	G A	
70:21.15mer1-15/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	
74	G A G	W I T F	H R R	H H D	R V L S	G A	
71:22.15mer1-16/0	GGGGCTGGGA	AGGCTATGTT	TAGTCATCT	TATCGTCATC	GGGGTTCGGC	TGGGGCC	SEQ ID NO.48
75	G A G	(K) A M (F)	(S) (H) S	Y R (H)	(R) G S A	G A	SEQ ID NO.49
72:23.15mer1-17/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC	
76	G A G	W I T F	H R R	H H D	R V L S	G A	

FIG. 7A





15MER1.SEQ

	10	20	30	40	50	60
73:24.15mer1-18/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC
77	G A G	W I T F	H R R	H H D	R V L S	G A
74:25.15mer1-19/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC
78	G A G	W I T F	H R R	H H D	R V L S	G A
75:26.15mer1-20/0	GGGGCTGGTT	CGATTACTTT	TCATCGTCGT	CATCATGATC	GTGTTCTTTC	TGGGGCC
79	G A G	W I T F	H R R	H H D	R V L S	G A

FIG. 7B